Page 62, line 10, after "(ATCC)" and before the comma "," insert the following: --on November 4, 1992--.

REMARKS

Entry of the foregoing and further and favorable reconsideration of the subject application pursuant to and consistent with 37 C.F.R. § 1.115 is respectfully requested.

Claims 1, 2, 4, 5 and 19-28 are currently pending.

By the present amendment, the specification has been amended so that the trademarks MILLI-Q and ALCONOX are identified by their generic terminology as well as being presented in capital letters and accompanied by the symbol for trademark registration (i.e., "®"). The specification has also been amended to indicate the date of deposit for ATCC accession number 69119 in accordance with the requirements of 37 C.F.R. § 1.808.

By the present amendment, Claim 19 has been amended to incorporate the limitations previously recited in canceled Claim 18. This amendment was necessary because Claim 19 originally depended from Claim 18. This amendment finds support in Claim 18 as originally filed in parent application Serial No. 08/149,099. Claim 20 has been amended to correct the dependency of this claim. This amendment was necessary in view of the cancellation of the claim from which Claim 20 originally depended (i.e., Claim 8). Claim 21 has been amended to change "transfection" to

--transfectoma-- to correct an inadvertent error. This amendment finds support at least in Claim 11 as filed in parent application Serial No. 08/149,099. No new matter has been added.

Turning now to the Official Action, the Examiner has maintained the provisional rejection of claims 1, 2, 4, 5 and 19-28 under the judicially created doctrine of obviousness-type double patenting as purportedly being unpatentable over claims 6-9 of copending application Serial No. 08/478,967.

As stated in the Reply and Amendment filed March 21, 1996, upon an indication that this case is otherwise allowable, Applicants will submit a Terminal Disclaimer to obviate this rejection.

The Examiner has maintained the provisional rejection of claims 19 and 20 under the judicially created doctrine of obviousness-type double patenting as purportedly being unpatentable over claim 18 of copending application Serial No. 08/475,813.

Upon an indication that this case is otherwise allowable, Applicants will submit a Terminal Disclaimer to obviate this rejection.

The Examiner has maintained his objection to the use of the trademarks "MILLI-Q" and "ALCONOX" because they are not capitalized and are not accompanied by their generic terminology (page 4, ¶ 19).

By the present amendment, Applicants have amended the specification in accordance with M.P.E.P. § 608.01(v) so that the trademarks are now identified by their generic terminology,

presented in capital letters and are accompanied by the symbol for trademark registration. This amendment should render this objection moot.

The Examiner notes that "Regarding applicants comments about submitting a new sequence listing, the Reff declaration establishes that Sequence Id no. 1 is correct, so that it is unclear as to why a new Seq. ID. listing would be needed" (Official Action, page 4, ¶ 20). Applicants understand the Examiner's statement to mean that the Reff Declaration sufficiently established that the additional nucleotide was an obvious error and that no new sequence listing is required.

The Examiner has maintained his rejection of claims 1, 2, 4, 5 and 19-28 under 35 U.S.C. § 112, first paragraph, as purportedly failing to adequately teach how to make and/or use the invention. Specifically, the Examiner has objected to the purported failure of the specification to recite the date of the deposit of ATCC accession number 69119 and the failure to satisfy the requirements of 37 C.F.R. § 1.808 regarding the conditions of the deposit for ATCC accession numbers 69119 and HB11388.

By the present amendment, Applicants have amended the specification so that it recites the date of deposit of ATCC accession number 69119. As the attached copy of the ATCC International Form of deposit indicates, the deposit of Anti-CD20 in TCAE 8 was received by the ATCC on November 4, 1992 and assigned ATCC accession number 69119 (see Exhibit A).

In addition, the undersigned hereby states that the deposits of ATCC accession numbers 69119 and HB11388 were made under the terms of the Budapest Treaty; and, that

1) access to the deposits will be available to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122, and

2) with the one exception as permitted in 37 C.F.R. § 1.808(b), that all restrictions imposed by the depositor on the availability to the public of the deposited biological materials will be irrevocably removed upon the granting of the patent.

In light of the amendment to the specification adding the date of deposit as well as the above statement regarding the conditions of deposits, withdrawal of this rejection is respectfully requested.

The Examiner has also maintained the rejection of Claims 19 and 20 under 35 U.S.C. § 103 as purportedly being unpatentable over Grossbard in view of Anderson et al. (1991).

As regards the primary reference of Grossbard et al., the Examiner states that "it would have been obvious to a routineer that a chimeric antiCD20 antibody could have been used for treating B cell lymphomas based on the art known advantages of chimeric over murine antibodies"; and, that "a routineer would have used a chimeric antibody in combination with a radiolabeled murine antibody because Grossbard et al. teach that radiolabeled chimeric antibodies would be therapeutically inferior to radiolabeled murine antibodies" (paragraph bridging pages 6-7).

The Grossbard et al. reference is a perspective article on monoclonal antibody-based therapies of leukemia and lymphoma. In contrast to the Examiner's statements directly supra, the Grossbard et al. article clearly demonstrates that one of ordinary skill in the art would not expect a particular chimeric antibody when administered in combination with a second radiolabeled antibody to be therapeutically effective in methods of treating B cell lymphoma. For example, in this regard, Grossbard et al. teach the following (emphasis added):

> 1) "Although much has been learned about critical characteristics of the antigen and antibody required for successful serotherapy, **the overall clinical results have been disappointing, with few sustained clinical responses observed.**" (page 863, column 1, second paragraph, last sentence).
>
> 2) "The past decade of clinical work has shown **numerous obstacles** to serotherapy (Table 1) secondary to the difficulty of delivering antibody to the tumor, the failure to kill all tumor cells, and the toxicity of serotherapy." (page 863, column 1, third paragraph, second sentence).
>
> 3) "The majority of clinical trials have been conducted using murine MoAbs [monoclonal antibodies]." (page 863, column 2, last paragraph, fourth sentence).
>
> 4) "Attempts to circumvent the antimurine antibody immune response have been undertaken using genetically restructured antibodies in which the rodent variable or hypervariable Ig regions are combined with human Ig genes to minimize the antigenic determinants. **These humanized antibodies may prove less immunogenic.**" (page 864, column 2, second paragraph, third sentence).
>
> 5) "Despite the promising preliminary results noted above [as regards radioimmunotherapy trials], **considerable controversy** exists concerning the optimal antibody, radionuclide, dose of antibody, and schedule of administration for future radioimmunotherapy trials." (page 871, column 1, last full sentence).

> 6) "Preliminary clinical studies with MoAbs in leukemias and lymphomas have **shed light on future directions for research**. Despite the low response rates with these therapies observed to date as single agents, the past several years have led to an explosive growth in the clinical knowledge base **upon which future trials can be constructed**." (page 874, column 2, fourth paragraph, first sentence)..

Based on the foregoing cites, it is clear that the Grossbard et al. reference teaches that the efficacy of using chimeric antibodies in methods of treating lymphoma is highly unpredictable. As noted supra, Grossbard et al. teach that humanized antibodies (i.e., human/rodent antibodies) "may prove less immunogenic"; and, that "low response rates" have been observed for treating lymphomas with monoclonal antibodies. Furthermore, Grossbard et al. state that there is "considerable controversy" about the optimum antibody to use in treating lymphomas and leukemias with radiolabeled antibodies. Thus, Grossbard et al. actually teach the highly unpredictable nature of using various types of monoclonal antibodies (e.g., natural, chimeric, radiolabeled) in methods for treating leukemia and lymphoma. This reference could be viewed as actually teaching away from the instant claimed invention. At the most, it must be viewed as an invitation to experiment. Furthermore, the Grossbard et al. reference indicates one skilled in the art would have no reasonable expectation of therapeutic success with any given antibody, chimeric or otherwise.

In contrast to the relatively negative predictions of Grossbard et al. regarding methods of using chimeric antibodies for treating lymphomas, the instant claimed invention discloses and

claims methods of using a particular chimeric anti-CD20 antibody which is both immunologically active **and** therapeutically effective when used to treat higher order mammals such as primates and humans. For example, the instant claimed antibody lysed human target cells through antibody-dependent cellular cytotoxicity demonstrating that the anti-CD20 antibody is immunologically active (section II.C.iii., page 45 and Figure 8). In addition, C2B8 infusion of macaque cynomolgus monkeys demonstrated that "significant depletion of B cell populations was achieved in peripheral lymph nodes and bone marrow when repetitive high doses of the antibody were administered"; and, that "even with such severe depletion of peripheral B lymphocytes during the first week of treatment, **no adverse health effects have been observed**" (page 56, lines 4-13) (emphasis added). Furthermore, Phase I/II single dose therapy studies of C2B8 conducted on fifteen human patients demonstrated that Peripheral Blood B Lymphocytes were depleted for all patients and that the depletion was maintained for in excess of two weeks (III.B.i., pages 56-57). Even still further, Phase I/II multiple dose therapy studies were underway at the time of filing (III.B.ii., pages 57-58).

In addition to the *in vitro* and *in vivo* studies discussed in the specification, the attached IDEC Pharmaceuticals Press Release dated May 21, 1996 (Exhibit B) reports on the preliminary analysis of a Phase III trial of IDEC-C2B8 as a single-agent treatment for relapsed low-grade or follicular non-Hodgkin's lymphoma. The press release states that "[O]f the first 48

evaluable patients, 23 responded to treatment with IDEC-C2B8, for an overall response rate of 47.9%"; and, that "[S]ix of these responses were complete responses (12.5%) and 17 were partial responses (35.4%)" (page 1, last paragraph). Furthermore, the press release states that the tumor marker gene bcl-2 "reverted from positive to negative in the peripheral blood of 12 of 16 patients analyzed, and in the bone marrow of six of 12 patients"; and, that "patients treated with conventional chemotherapy alone do not become bcl-2 negative in the bone marrow" (page 2, first paragraph). These results confirmed those obtained in the previous Phase II study of IDEC-C2B8 (page 2, second paragraph).

Even further still, the second Anderson Declaration states that the C2B8 antibody "**has been shown to be highly effective** in treating patients with relapsed low grade lymphoma, **producing marked response rates in very sick patients**" (page 2, fourth full paragraph) (emphasis added).

Thus, it clearly **would not** have been obvious to a "routineer" that the chimeric antibody of the instant claimed invention would have been effective when administered to human patients, especially in view of the statements in the Grossbard et al. reference which suggest that such a result would be quite unexpected for a chimeric murine human antibody, administered with or without a second radiolabeled antibody. Clearly, the Grossbard et. al. reference **does not** provide sufficient teaching as to how one of ordinary skill would obtain the particular chimeric antibody of the instant application, or that the claimed

antibody would be therapeutically effective when used in methods for treatment of B cell lymphoma.

The Examiner also relies on the Anderson et al. (1991) abstract for a secondary reference in this rejection. This abstract is a brief recitation of on-going research as regards a C2B8 antibody. However, this abstract is not an enabling prior art disclosure since the public was not in possession of the claimed invention prior to the filing of this application. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 226 U.S.P.Q. 619 (Fed. Cir. 1985). Here, one of ordinary skill in the prior art **could not** have combined the abstract's general and brief description of a chimeric antibody with his own knowledge to make the claimed novel chimeric antibody with its unique properties. As discussed immediately supra, the specific chimeric antibody claimed in the instant application has unexpected and unique immunological and therapeutic properties. Furthermore, the primary reference relied on by the Examiner teaches that "humanized antibodies may prove less immunogenic"; that "considerable controversy exists concerning the optimal antibody"; and, that such therapies have produced "low response rates". Based on the teachings of Grossbard et al. as regards the unpredictability of using any particular chimeric antibody for immunological and therapeutic purposes, the Anderson et al. (1991) abstract clearly **did not** place the instant claimed inven-

tion in the hands of the public. Therefore, one of ordinary skill in the art **could not** have combined the teachings of this abstract with his own knowledge and produced the instant claimed chimeric antibody with its unusual and unpredictable properties. Thus, the Anderson et al. (1991) abstract is a non-enabling disclosure which does not constitute a proper basis for a prior art rejection of treatment methods using the specific chimeric antibody as claimed in the instant application.

The Examiner has also stated that "the Anderson declaration submitted 3/21/96 seems to indicate that the claimed chimeric antibody was not available other than to the authors of the Anderson et al. publication"; and, that "the Anderson et al. abstract is prior art in that it was known by others (eg. the noninventor authors of the Anderson et al. publication)" (Official Action, page 7, first paragraph). The Examiner further states that "Applicant is advised that this rejection can be overcome by a Katz type declaration". Id. Applicants hereby present a first executed Declaration by Darrell R. Anderson filed under 37 C.F.R. § 1.132 in copending, commonly owned U.S. Patent Serial No. 08/149,099 which clearly establishes that the additional co-authors Robert E. McCoobery and Syamal Raychaudhuri merely acted under the direction of Darrell R. Anderson (i.e., the first-listed inventor of the instant application) and thus they did not contribute to the conception of the invention disclosed and claimed in the instant patent application. In contrast, the remaining abstract co-authors (Darrell R. Anderson,

Mitchell Reff, Roland Newman and Nabil Hanna) each contributed to the conception of the instant claimed invention. In light of this Declaration, the Anderson et al. (1991) abstract clearly describes Applicants' own work. Thus, this Declaration establishes that the chimeric antibody disclosed in the cited abstract **was not** "known by others" and not available to the public prior to the filing of the instant application. If the claimed chimeric antibody was not available to the public, then clearly one of ordinary skill in the art could not have used the novel antibody in the claimed methods of treating B cell lymphoma.

In summary, the Grossbard et al. reference is, at most, an invitation to experiment. As discussed supra, the Grossbard et al. reference provides **no** guidance as to how one of ordinary skill in the art would obtain a chimeric anti-CD20 antibody with the unexpected immunological and therapeutic properties of the instant claimed invention. In addition, one of ordinary skill in the art would have no reasonable expectation of success in obtaining the claimed novel chimeric antibody and of using the antibody in effective therapeutic methods of treating B cell lymphoma, especially in view of the teachings of Grossbard et al. regarding the lack of progress in this area of research. Thus, successful methods of using the claimed chimeric antibody to treat B cell lymphoma would also be unexpected and unobvious. Furthermore, the Anderson et al. (1991) abstract is non-enabling prior art which clearly did not put the specific and novel claimed chimeric antibody in the possession of the public. Even

furthermore, the first Anderson Declaration establishes that the chimeric antibody disclosed in the cited abstract was not available to the public prior to the filing of this application. For these reasons, withdrawal of this rejection is respectfully requested.

The Examiner has also maintained the rejection of Claims 1, 2, 4, 5, and 21-28 under 35 U.S.C. § 103 as purportedly being unpatentable over Robinson et al. (WO 88/04936) in view of Anderson et al. (1991). The Examiner states that "Applicant is advised that this rejection can be overcome by a Katz type declaration" (Official Action, page 8, first paragraph, last sentence).

The Examiner relies upon the Anderson et al. (1991) reference as the secondary reference in this rejection. Applicants herein incorporate the arguments presented supra in response to the § 103 rejection of Claims 19 and 20 over Grossbard et al. in view of Anderson et al. (1991). As indicated previously, the first Anderson Declaration clearly establishes that the Anderson et al. (1991) abstract describes Applicants' own work and is therefore removed as a 35 U.S.C. 103 prior art publication against the instant claimed invention. Applicants further note that the date of the Anderson et al. (1991) abstract is December 16-18, 1991 while the instant application is a continuation-in-part of United States Serial No. 07/978,981 which was filed on November 13, 1992. Moreover, all of the subject method claims cited in this rejection have their basis in the 07/978,981 application. Therefore, the abstract predates the effective filing

date of the instant application by less than one year and is **not** available as § 102(b)/103 art. In light of this Declaration, the Anderson et al. (1991) abstract describes Applicants' own work and is therefore removed as a 35 U.S.C. § 102(a)/103 prior art publication against the instant claimed invention.

The Examiner also relies upon Robinson et al. (WO 88/04936) as the secondary reference in this rejection. Since discussion of the Robinson et al. reference is unnecessary given that the secondary reference is no longer applicable, the Robinson et al. article will be addressed in detail in the following rebuttals to the prior art rejections which rely on Robinson et al. as the primary reference. Furthermore, because the secondary reference of this rejection is no longer available as prior art, Applicants respectfully request the withdrawal of this rejection.

The Examiner next newly rejected claims 19 and 20 under 35 U.S.C. § 112, second paragraph, as purportedly being indefinite in that they both depend on cancelled claim 18. By this amendment, claim 19 has been rewritten in independent form and now includes all of the limitations of previously canceled claim 18. In addition, claim 20 has been amended so as to now depend directly from claim 19. These amendments should render this rejection moot.

The Examiner next newly rejected claims 1, 2, 4, 5, and 21-28 under 35 U.S.C. § 103 as purportedly being unpatentable over Robinson et al. (U.S. Patent 5,500,362) (the Robinson Patent).

This rejection is respectfully traversed for the following reasons.

The Examiner asserts that "the species of antibody recited in the claim is encompassed by the generic antibody taught by Robinson et al." (Official Action, page 9, lines 13-14). The Examiner further alleges that:

1. "There appears to be no functional difference between the chimeric antibody of claim 1 of Robinson et al. and the antibody of the instant invention" (page 9, lines 16-18);

2. "It would have been obvious to a routineer that such a chimeric antibody would be administered in an art known pharmaceutically acceptable carrier administered, because [the chimeric 2H7] antibody was to be administered to humans" (page 9, lines 24-27);

3. "A routineer would have arrived at the concentration of antibody specified in the claims because said claims encompass a dose at which a therapeutic effect would have been expected" (page 9, lines 27-29); and,

4. "a routineer would have produced the antibody of the instant invention or a functional equivalent using routine experimentation" (page 8, lines 22-23).

Each of these assertions by the Examiner will be shown to be without foundation in the following comparisons between the chimeric antibody of the Robinson Patent (the chimeric 2H7 anti-

body) and the anti-CD20 antibody (IDEC-C2B8) of the instant claimed invention.

<u>There is a clear functional difference between the Robinson chimeric 2H7 antibody and the chimeric IDEC-C2B8 antibody of the instant invention.</u>

The Robinson patent provides very little disclosure as regards the functionality of the chimeric 2H7 antibody. However, the Robinson patent does state that "the chimeric 2H7 antibody binds to (Bp35 (CD20)) antigen positive human B cells to approximately the same extent as the mouse 2H7 monoclonal antibody" (column 19, lines 58-61).

In contradistinction to the Robinson patent, the instant specification provides numerous sources of evidence which clearly indicate that the functionality of the chimeric mouse human monoclonal antibody C2B8 differs in its binding affinity when compared to the murine monoclonal antibody 2B8 used in the development of C2B8. For example, the specification of the instant invention demonstrates that C2B8 was evaluated for human C1q binding by flow cytometry; and, that when C2B8 was incubated with SB cells followed by the addition of fluorescein-labeled C1q, that a significant increase in fluorescent intensity was observed. In contrast, under the same conditions, murine-2B8 antibody, as well as an irrelevant human IgG1 both failed to bind human C1q (see section II.C.i., page 44 and Figure 6). C1q is obtained from human serum and combines with Antibody:Antigen complexes but not with free Antibody or Antigen. Thus, the

chimeric mouse human C2B8 antibody shows a greater binding affinity for human C1q than the murine antibody used to develop it. Quite clearly, the fact that a chimeric antibody would be obtained having enhanced antigen-binding affinity in relation to the parent murine antibody would not have been suggested by the Robinson patent.

Furthermore, C2B8 has also been tested for its ability to lyse lymphoma cell lines in the presence of human serum as a source of complement. Approximately 50% of the SB target cells were lysed under the testing conditions. In contrast, no significant lysis was observed in experiments using $CD20^+$ SB cells incubated with murine-2B8 antibody (see section II.C.ii., pages 44-45 and Figure 7). This provides further evidence that the chimeric C2B8 antibody has a different binding affinity than the murine 2B8 antibody from which it was developed.

Furthermore, the second executed Anderson Declaration filed in copending U.S. Serial No. 07/149,099 provides additional evidence of the unique binding properties of the chimeric C2B8 antibody. The second Anderson Declaration states that "IDEC-C2B8 has exceptionally strong binding to low affinity FcγRII receptors, in contrast to the positive control human IgG1 isotype and the negative control human IgG4 isotype" (page 3, last sentence and Figure 1). The second Anderson Declaration further states (page 4, first paragraph and paragraph bridging pages 4-5) (emphasis added):

> "In my expert opinion, these results are unexpected, in view of the fact that low affinity receptor

binding by antibodies is usually reduced in the absence of antigen binding. By contrast, these results indicate that **IDEC-C2B8 has an unusually strong affinity** for this type of receptor which may be even further enhanced *in vivo* on binding of antigen. The results are highly supportive of the claim that IDEC-C2B8 can mediate effector cell functions *in vivo* with effector cells expressing FcγRII receptors in a manner unequaled by other CD20 antibodies. Moreover, these results suggest that **this antibody does not function equivalently to other chimeric anti-CD20 antibodies.**

In my opinion, it would be highly unreasonable to expect that other anti-CD20 antibodies including the chimeric antibodies of the Robinson et al., if compared in this assay, would show equivalent behavior especially because comparison to totally human antibodies of the same isotype as seen in the controls, are not equivalent. In fact, the murine antibody from which the variable region was derived shows no more binding in this assay than the negative control above. Therefore, the subject chimeric antibody shows behavior uncommon to any other antibody tested including other chimeric engineered constructs which differ from C2B8 only in the variable region which is contained therein. This property, therefore, appears to be attributable to the particular variable region contained in the C2B8 antibody. However, it is noted that the assay shown above does not measure or in any way relate to antigen specificity, only the ability to bind to human FcRII receptors. In my opinion, it is this property that is the most unique of the C2B8 effector properties, and may explain the unparalleled ability of the subject antibody to mediate such extensive depleting behavior, *in vivo*. As a expert in the art, I can well attest to the fact that type II receptor binding mediated through macrophages and monocytes following specific antibody binding to target cells, is well regarded by many skilled in the art to be the most potent of all possible *in vivo* depleting mechanisms."

These studies demonstrate that the ability of C2B8 to bind human C1q, to mediate complement-dependent cell lysis of human B-lymphoid cell lines, and to bind to low affinity FcγRII receptors dramatically differs from the ability of murine 2B8 antibody to accomplish these same functions and also to the other chimeric anti-CD20 antibodies to which it was compared. In direct con-

trast to the results obtained with the C2B8 of the instant invention, the Robinson patent only states that "the chimeric 2H7 antibody binds to (Bp35 (CD20) antigen positive human B cells to approximately the same extent as the mouse 2H7 monoclonal antibody" (column 19, lines 58-61). Thus, by the patentees' own admissions, their chimeric antibody only exhibited approximately the same affinity as the parent murine antibody from which it was derived.

Thus, there is a clear functional difference between the Robinson chimeric 2H7 antibody and the chimeric IDEC-C2B8 antibody of the instant invention.

It would not have been obvious to a routineer that the C2B8 could be administered in an art-known pharmaceutically acceptable carrier administered to humans with therapeutic effects.

Although the Robinson patent suggests that the disclosed antibodies can be used for therapeutic purposes by themselves (column 13, lines 31-33), the patent also states the following regarding the use of the chimeric 2H7 antibody for the treatment of human disease (column 20, lines 8-20):

> "The therapeutic efficacy of mouse monoclonal antibodies (which are the ones that have been tried so far) appears to be too low for most practical purposes. Because of the "human" properties which may make the chimeric 2H7 monoclonal antibodies more resistant to clearance and less immunogenic in vivo, the chimeric 2H7 monoclonal antibodies will be advantageously used not only for therapy with unmodified chimeric antibodies, but also for development of various immunoconjugates with drugs, toxins, immunomodulators, isotopes, etc., as well as for diagnostic purposes such as in vivo imaging of B-cell tumors (for example, lymphomas and leukemias) using appropriately labelled chimeric 2H7 antibodies."

Thus, the Robinson patent actually indicates that: 1) one of ordinary skill in the art would have reason to believe that the chimeric 2H7 antibody may not be therapeutically effective due to its "murine properties"; and, 2) that the chimeric 2H7 antibody would not be therapeutically effective without additional unmodified chimeric antibodies and/or one or more immunoconjugates. Furthermore, while the Robinson patent speculates that their chimeric 2H7 antibody **"may"** be used for the treatment of diseases such as B cell disorders, these statements must be viewed as no more than a mere suggestion to those in the art to determine whether or not this suggestion is accurate for this particular antibody, particularly because the reference **lacks any data** to support an assertion of therapeutic effectiveness, and even more importantly, it also lacks any data using higher order mammals such as primates or humans.

In contrast, the specification of the instant application is replete with data to indicate that the chimeric C2B8 antibody is both immunologically active **and** therapeutically effective when used to treat higher order mammals such as primates and humans. For example, in addition to mediating complement-dependent cell lysis of human B-lymphoid cell lines as discussed supra, the instant claimed antibody also lysed human target cells through antibody-dependent cellular cytotoxicity demonstrating that the anti-CD20 antibody is immunologically active (section II.C.iii., page 45 and Figure 8). In addition, C2B8 infusion of macaque cynomolgus monkeys demonstrated that "significant depletion of B

cell populations was achieved in peripheral lymph nodes and bone marrow when repetitive high doses of the antibody were administered"; and, that "even with such severe depletion of peripheral B lymphocytes during the first week of treatment, **no adverse health effects have been observed**" (page 56, lines 4-13) (emphasis added). Furthermore, Phase I/II single dose therapy studies of C2B8 conducted on fifteen human patients demonstrated that Peripheral Blood B Lymphocytes were depleted for all patients and that the depletion was maintained for in excess of two weeks (III.B.i., pages 56-57). Even still further, Phase I/II multiple dose therapy studies were underway at the time of filing (III.B.-ii., pages 57-58).

In addition to the *in vitro* and *in vivo* studies discussed in the specification, the attached IDEC Pharmaceuticals Press Release dated May 21, 1996 (Exhibit B) reports on the preliminary analysis of a Phase III trial of IDEC-C2B8 as a single-agent treatment for relapsed low-grade or follicular non-Hodgkin's lymphoma. The press release states that "[O]f the first 48 evaluable patients, 23 responded to treatment with IDEC-C2B8, for an overall response rate of 47.9%"; and, that "[S]ix of these responses were complete responses (12.5%) and 17 were partial responses (35.4%)" (page 1, last paragraph). Furthermore, the press release states that the tumor marker gene bcl-2 "reverted from positive to negative in the peripheral blood of 12 of 16 patients analyzed, and in the bone marrow of six of 12 patients"; and, that "patients treated with conventional chemotherapy alone

do not become bcl-2 negative in the bone marrow" (page 2, first paragraph). These results confirmed those obtained in the previous Phase II study of IDEC-C2B8 (page 2, second paragraph).

Even further still, the second Anderson Declaration states that the C2B8 antibody "**has been shown to be highly effective** in treating patients with relapsed low grade lymphoma, **producing marked response rates in very sick patients**" (page 2, fourth full paragraph) (emphasis added).

Thus, it clearly **would not** have been obvious to a "routineer" that the chimeric antibody of the instant claimed invention would have been effective when administered to human patients in a pharmaceutically acceptable carrier, especially in view of the statements in the Robinson patent which suggest that such a result would be quite unexpected for a chimeric murine human antibody. At best, the Robinson patent would provide an invitation to attempt to obtain chimeric antibodies with specific functionalities, wherein such antibodies possibly can be administered in pharmaceutically acceptable carriers. An "obvious-to-try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 14 U.S.P.Q. 1741, 1743 (Fed. Cir. 1990). Clearly, the Robinson patent **does not** provide sufficient teaching as to how one of

ordinary skill would obtain the particular chimeric antibody of the instant application, or that the claimed antibody would be therapeutically effective when administered in pharmaceutically acceptable carriers.

One of ordinary skill in the art would not have arrived at the concentration of antibody specified in the claims because said claims encompass a dose at which a therapeutic effect would not have been expected.

As indicated above, the Robinson patent provides **no** information regarding the treatment of humans with chimeric 2H7 antibody. Nor does the Robinson patent provide any information as regards treatment of any non-human primate with chimeric 2H7. Furthermore, the Robinson patent is **completely silent** as regards the concentration of any chimeric murine human antibody which would produce a therapeutic effect on humans. Instead, the Robinson patent merely makes several prophetic statements about possible therapeutic uses of 2H7 (*See*, e.g., column 20, lines 8-20). Clearly, such prophetic statements are merely an invitation to experiment.

In contrast, as recited supra, the instant disclosure provides detailed information regarding the therapeutic uses of C2B8, including actual concentrations of the antibody used in successful human clinical trials. Additional information has been provided via the IDEC Press Release and the second Anderson Declaration. In addition, the second Anderson Declaration states

the following regarding dosage levels (paragraph bridging pages 2-3) (emphasis added):

> "THAT, while many of the *in vitro* properties of IDEC-C2B8 are shared with other anti-CD20 antibodies, a remarkable and apparently unique property of IDEC-C2B8 is the ability to deplete CD20 positive cells *in vivo* with such low doses. **As low as 0.4 mg/kg was effective** in depleting better than 95 percent of B cells in the peripheral blood of monkeys. This was a surprising result which supports the claims that **C2B8 has unique properties beyond what is shared by other anti-CD20 antibodies**. While it is difficult to compare directly other chimeric anti-CD20 antibodies because none have been tested *in vivo* as extensively as C2B8, the available evidence would suggest that C2B8 has a much stronger effector depleting property than other chimeric antibodies which is apparently attributable to **exceptionally strong Fc receptor binding.**"

Thus, the second Anderson Declaration clearly establishes the highly unexpected result that the chimeric C2B8 antibody is effective at extremely low concentrations. Therefore, one of ordinary skill in the art clearly would not have arrived at the concentration of antibody specified in the claims.

<u>One skilled in the art would not have produced the C2B8 antibody of the instant invention or a functional equivalent using routine experimentation.</u>

As an example of the prior art, Watson et al. (1992) (Exhibit C) teach that "[T]he first method used to reduce the immunogenicity of a mouse monoclonal antibody was simply to construct *chimeric* genes that encoded proteins in which the variable regions from the mouse antibody where fused to the constant regions from a human antibody" (page 464, sentence bridging columns 1-2). Watson et al. also teach the following regarding such "humanized" antibodies (paragraph bridging pages 464-465):

> "This antibody, however, was not fully *humanized*, because it retained amino acid sequences from the mouse protein. Thus, scientists have set out to engineer fully humanized monoclonal antibodies that will be indistinguishable from natural molecules. Extensive studies of the three-dimensional structures of antibody molecules tell us that only a few of the one hundred amino acids in the variable region of an antibody actually contact the antigen; these regions of contact are referred to as *complementarity determining regions* (CDRs). Three CDRs each comprise the antigen-binding sites on the light and heavy chains. The rest of the variable region serves as a scaffold to anchor the CDRs in the correct positions. This breakdown of amino acids in the variable region into those serving recognition and those serving structural roles is also evident from simply comparing the sequences of many antibody molecules. Amino acid sequences in the CDRs are *hypervariable*, whereas the structural, or *framework*, amino acids differ little.
>
> Thus, to make a fully humanized antibody, all that would be required in principle would be to use in vitro mutagenesis to transfer the CDR amino acid sequences from a mouse [monoclonal antibody] to a natural human antibody."

This excerpt from Watson et al. establishes that: 1) chimeric mouse human antibodies were <u>not</u> preferable at the time of the instant invention because they were not "fully humanized"; and, 2) the amino acid sequences of CDRs are "hypervariable".

Robinson et al. (<u>Hum. Antibod. Hybridomas</u>, 2:84-93, 1991) (see previous Information Disclosure Statement) teach two chimeric mouse human antibodies (ING-1 and ING-2) constructed from anti carcinoma mouse hybridomas. Robinson et al. also teach the following (page 91, column 2, last paragraph):

> "[W]e initially expected that the human IgG1 Fc region in the chimeric antibodies would mediate strong in vitro ADCC [antibody-dependent cellular cytotoxicity] and CDC [complement-dependent cytolysis] activities, as has been previously observed for other chimeric mouse-human antibodies. Although the ING-1 antibody has moderate CDC activity against a colon carcino-

> ma cell line (HT-29), neither ING-1 nor ING-2 mediated CDC of the breast carcinoma cell lines tested."

Therefore, one of ordinary skill in the art could not predict the specificity or therapeutic value of a particular chimeric mouse human antibody without testing it extensively. Furthermore, the combined teachings of Watson et al. and Robinson et al. (1991) teach that each chimeric antibody has unique binding properties which can only be ascertained through rigorous testing.

The Robinson Patent does not provide any guidance as to how one of ordinary skill in the art overcomes the challenges discussed by Watson et al. and Robinson et al. (1991) regarding actual chimeric antibody specificity and therapeutic value. Furthermore, the Robinson patent merely provides a general method for producing chimeric mouse human antibodies and further discloses one specific chimeric antibody (2H7) produced by such a method. The Robinson patent does not provide any teaching as regards how one of ordinary skill in the art would produce chimeric mouse human antibodies which have specific mouse CDRs so as to more fully "humanize" the chimeric antibodies. Even furthermore, the Robinson patent provides **no information** as regards the actual therapeutic use of chimeric 2H7, as discussed supra. Based on the prior art teaching and the disclosure of the Robinson patent, one of ordinary skill in the art would have no reason to believe that the functional characteristics of chimeric 2H7 and C2B8 are similar. Thus, one of ordinary skill in the art

would not look to the Robinson patent to produce the unique C2B8 antibody of the instant claimed invention.

The second Anderson Declaration clearly establishes that the C2B8 antibody of the instant claimed invention "**shows behavior uncommon to any other antibody tested** including other chimeric engineered constructs which are different from C2B8 **only in the variable region**" (page 4, lines 15-18) (emphasis added). The Robinson patent and other pertinent prior art **do not** provide any guidance as to how one of ordinary skill in the art would obtain a chimeric antibody with the unique properties of C2B8. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The burden is on the Patent Office to substantiate an inherency based obviousness rejection. In the instant case, the Examiner has not met his burden because of the inherent unpredictability of the properties of any given chimeric antibody as established by the second Declaration of Anderson as well as the prior art cited by the Examiner. Therefore, there is no reasonable basis to conclude that the chimeric antibody disclosed by the Robinson patent is functionally equivalent to the subject chimeric anti-CD20 antibody, especially based on the § 1.132 Declaration which demonstrates that the therapeutic properties of chimeric antibodies are not only a function of antigen binding, but rather depend upon other factors, in particular the specific variable sequence of the antibody.

In summary, the above discussion establishes that: 1) one of ordinary skill in the art would reasonably expect, absent evidence to the contrary, that there is a functional difference between the chimeric antibodies taught by the Robinson patent and the chimeric antibody of the instant claimed invention; 2) one of ordinary skill in the art could not have expected that a chimeric mouse human antibody such as C2B8 would be directly useful as therapeutic agent; 3) one of ordinary skill in the art would not have expected C2B8 to be effective at the low concentrations disclosed as being effective in the instant application; and, 4) one of ordinary skill in the art would not have been able to produce the unique C2B8 antibody of the instant invention using routine experimentation.

In addition, Applicants advance that the claims in the counterpart European Patent Application No. 94901444.3 cover the same subject matter as claimed in the instant patent application and have been allowed. While the U.S. Examiner is not bound by the decision of the European Patent Office, this is provided as further evidence of the novelty and non-obviousness of the instant claimed invention. For all of the above reasons, withdrawal of this rejection is respectfully requested.

The Examiner next newly rejected claims 1, 2, 4, 5 and 21-28 under 35 U.S.C. § 103 as purportedly being unpatentable over Robinson et al. (WO 88/04936). This rejection is respectfully traversed for the reasons set forth below.

WO 88/04936 claims priority based upon a U.S. Patent application which is a parent of U.S. Patent No. 5,500,363, the subject of the above-discussed rejection over the Robinson patent. Thus, the specification of WO 88/04936 is virtually identical to the specification of the Robinson patent. In fact, the Examiner's rejection over WO 88/04936 reads the same as the rejection over the Robinson patent, with the exception of cited pages, lines, etc. Therefore, Applicants herein incorporate all of the arguments stated immediately above for the response to the instant rejection over WO 88/04936.

For the reasons stated supra, withdrawal of this rejection is respectfully requested.

The Examiner next newly rejects claims 19 and 20 under 35 U.S.C. § 103 as purportedly being unpatentable over Robinson et al. (US Patent 5,500,362) or Robinson et al. (W) 88/04936) as applied to claims 1, 2, 4, 5 and 21-28 and further in view of Grossbard et al.

Applicants have fully addressed each of the Robinson et al. references in previous rejections over these references. Therefore, Applicants herein incorporate all of the arguments stated above in response to the previous rejections over each of the Robinson et al. references (i.e., U.S. Patent 5,500,362 and WO 88/04936). Furthermore, Applicants have also fully addressed the Grossbard et al. reference in a previous rejection and herein incorporate the arguments stated above in response to this reference. As Applicants' comments have clearly indicated, the in-

stant claimed methods of administering the specific claimed chimeric antibody in conjunction with a radiolabeled anti-CD20 antibody would not have been obvious to one of ordinary skill in the art at the time of the invention.

For the reasons stated supra, withdrawal of this rejection is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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By _____

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